Bandolier 88

What do we think?
What do we know?
What can we prove?

Evidence-based health care **£3.00** **June 2001 Volume 8 Issue 6**

EBANDOLIER

Weekly visitors to ***Bandolier's*** electronic resource now number almost 90,000, so here is an update on electronic expansion. New electronic content is 3-4 times more extensive than it is on paper. There is every issue of ***Bandolier*** in downloadable format, a searchable database, and masses of stuff where we've gathered together useful information and evidence. And it's **FAST**, so no boring waiting.

The survey in ***Bandolier*** 85 was helpful in moulding our plans. With the other "market research", it helps keep us relevant. As a result, we hope to launch an AF site in July, an arthritis site in July/August, and a "genetics for idiots" expansion later in the year. In the meantime:

Palliative and Supportive Care is the first response to your feedback. This is being developed with the Cochrane PaPaS SRG, and with support from the BUPA foundation. Tricky territory, but there's much to do.

Migraine has been expanded in a major way, and is now looking much as we want it to. It has a raft of new systematic reviews on various treatments.

Managing to make a difference now has a series of three web essays on managing to make a difference. This has been the top section for visits over the past month, and has nearly 200 individual stories that could be helpful. There are more abstracts of useful literature.

Healthy living grows using ***Bandolier***'s own resources. There are new sections on alcohol (which type is best for better health) and on obesity. In the next month we will be updating ***Bandolier***'s 10-tips for healthy living in response to more evidence, and including a section on how to lose weight.

Complementary and alternative therapy has been updated with evidence from more reviews. Some work, many don't, and there's harm as well as (sometimes) benefit. Probably the most comprehensive bundle of evidence on CAT to be found on the web.

Diagnostics and diagnosis is in the process of expansion over the next month. Look out for web essays and extracts from papers with good diagnostic information.

Vaccines, again in response to readers' requests pulls together as much as we can, especially all the stuff on MMR. As time and resources permit, we'll expand it.

email updates

Once a month you can have an email to give you a link to each new story in ***eBandolier***. Just email bandolier@pru.ox.ac.uk and ask for it. We will never give these email addresses to anyone else.

EVEN MORE ON MMR

Previous issues of ***Bandolier*** (84 and 86) have addressed the safety of MMR vaccines, with strong evidence that there is no link between MMR and autism or between MMR and inflammatory bowel disease. But because concerns were so strong, it is valuable to return to the subject when even more powerful evidence concerning connections between MMR and childhood illness becomes available. Two more studies provide additional reassurance.

Measles vaccines and inflammatory bowel disease

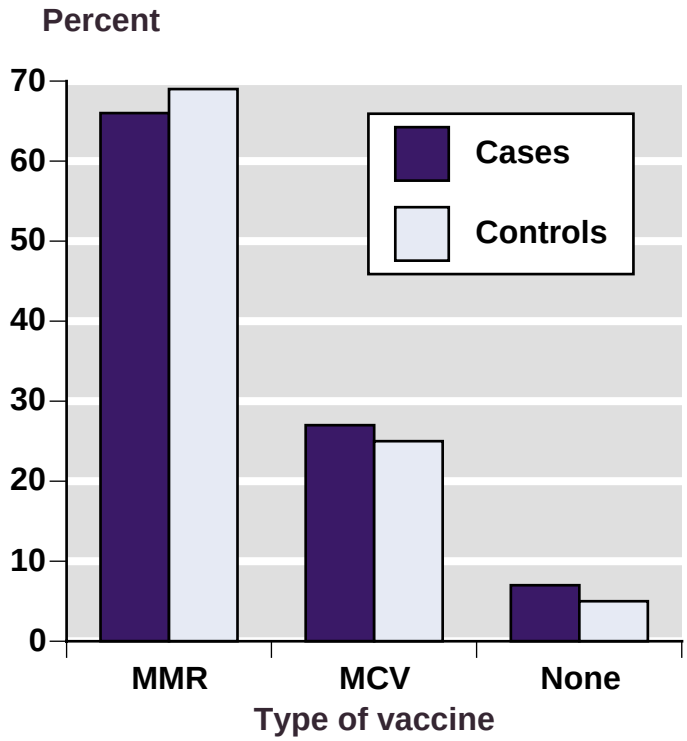
This study [1] was conducted in the USA on the populations of four health maintenance organisations as part of a vaccine safety programme coordinated by the Centres for Disease Control and Prevention. In each of the HMOs trained medical abstractors reviewed medical records using a standardised instrument. Cases were individuals enrolled since birth (1958 was the earliest date) to 1989. Consistent criteria were used for definite and probable diagnosis of Crohn's disease, ulcerative colitis, or unspecified irritable bowel disease. This involved diagnosis by a gastroenterologist, with signs and symptoms and a diagnostic test for irritable bowel disease. Five controls were selected for each case, matched by sex, HMO and birth year. Dates of vaccination, type of vaccine, and date of diagnosis were also recorded.

Results

There were 155 cases of irritable bowel disease, with 152 definite or probable cases. Seven cases had no discernible onset date, two were of unspecified disease, and one was vaccinated when older than 10 years, leaving 142 cases and 432 controls for analysis.

In this issue

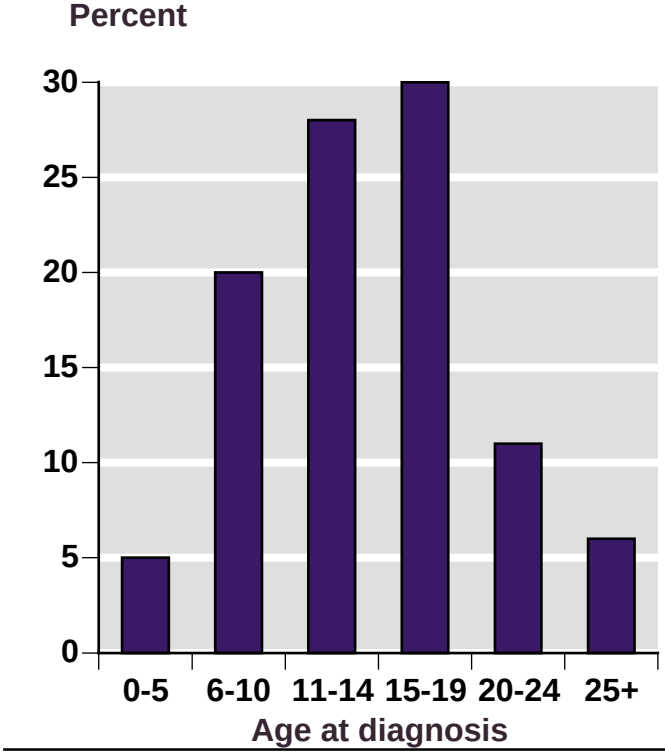
Figure 1: Type of vaccine used



Most had been vaccinated. Figure 1 shows the percentages vaccinated with MMR, with a measles-containing vaccine (MCV) or who were not vaccinated. The age at IBD diagnosis ranged from under five years to over 25 years (Figure 2).

The risk of inflammatory bowel disease was the same for vaccinated or unvaccinated people, split by type of vaccine or Crohn's disease or ulcerative colitis. There was an average of about 140 months between vaccination and diagnosis for cases and vaccination and control reference date for controls. Only 1% of cases developed inflammatory bowel disease within a year of vaccination and only 1% of controls developed inflammatory bowel disease within a year of vaccination.

Figure 2: Age at diagnosis of IBD



Looking at whether children were vaccinated before 12 months, between 12 and 18 months, or after 18 months showed no difference in the risk of developing inflammatory bowel disease.

Autism, MMR and GP visits

A UK study examined the rates of GP consultation before and after MMR vaccination in children who became autistic and in controls [2]. It used the Doctor's Independent Network, a computerised database covering a million patients in 127 practices providing lifelong medical histories for children remaining with the practice from birth.

Figure 3: GP visits and vaccination - 2 months

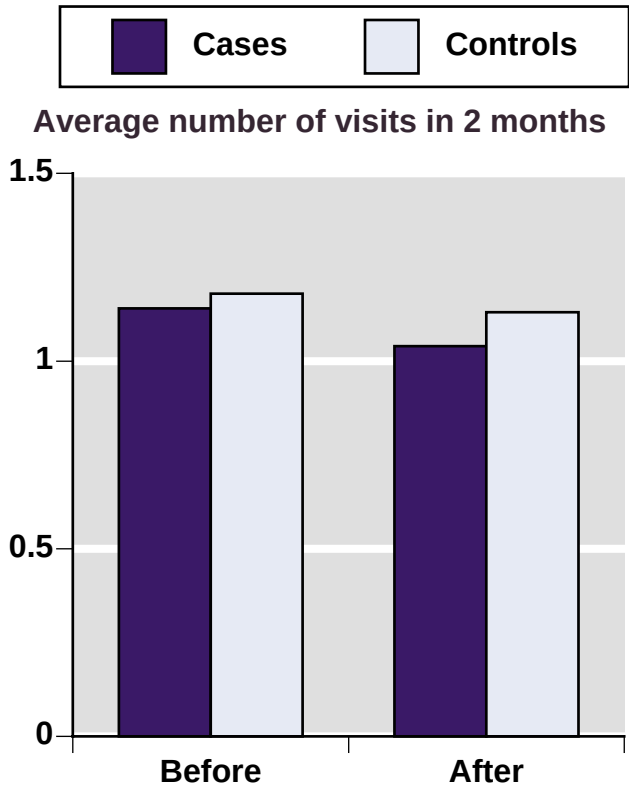
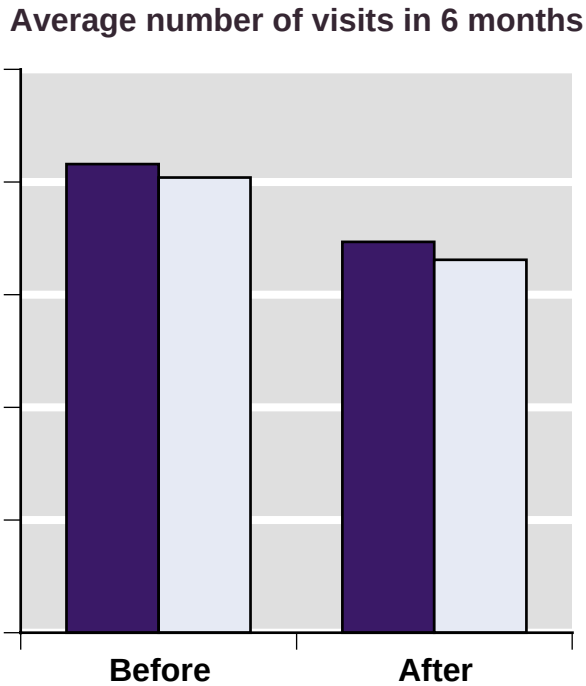


Figure 4: GP visits and vaccination - 6 months



There were 79 cases with a diagnosis of autism, but one was immunised with MMR after autism was diagnosed, and seven were never immunised. That left 71 cases for analysis, with four controls chosen for each matched by age, sex, month of immunisation and practice.

Results

There was no difference in the number of visits in the two months (Figure 3) or six months (Figure 4) before or after MMR vaccination for cases or controls.

Comment

These are two excellent studies. They were both conducted on defined populations. They examined clinically important issues, either defined diagnosis of inflammatory bowel disease, or visits to GPs that could reflect a change in parental concern. In neither case was there any link with MMR vaccination.

One of the papers [1] has a superb discussion of methodological issues and history of the linkage between concern over MMR safety and the evidence. Both explain why the fears arose out of methodologically flawed studies.

Parents, and their physicians, can be reassured that high quality studies conducted around the world continue to demonstrate that there is no link between MMR and autism or inflammatory bowel disease. The weight of evidence on the safety of MMR is now rather large. The evidence in support of a link is incredibly weak.

A further thought is that there may just be the germ of an interesting paper or thesis in all this, examining the chronology of the scare in relation to the evidence available. There are lessons to be learned, certainly by news reporters, certainly by editors of learned journals and their peer reviewers, and probably by providers of healthcare. Disproving a negative is always going to be difficult, but knowing that good efficacy and safety assessment measures are in place for early warning is of major public importance.

References:
1 RL Davis et al. Measles-mumps-rubella and other measles-containing vaccines do not increase the risk of inflammatory bowel disease. Arch Pediatr Adolesc Med 2001 155: 354-359.
2 S DeWilde et al. Do children who become autistic consult more often after MMR vaccination? British Journal of General Practice 2001 51: 226-227.
3 see also www.nap.edu

QUININE FOR NOCTURNAL LEG CRAMPS

Analysing visits to the ***Bandolier*** Internet site showed that quinine and nocturnal leg cramps (***Bandolier*** 12) was one of the most frequently viewed pages. So we sought any more recent information since a meta-analysis published in 1995. A second meta-analysis [1] was published in 1998, and was interesting because it included unpublished material and provided some empirical evidence of publication bias.

Review

Searching using three computerised databases was up to July 1997. Unpublished data was found through examining an FDA report, enquiries to British and German regulatory authorities, and pharmaceutical companies.

For inclusion studies had to be randomised and double blind, and to be in ambulatory patients. Information was abstracted on age and sex of patients, treatment duration, outcome measures, adverse effects and washout periods. The main efficacy outcome was the reduction in nocturnal leg cramps in a four-week period, severity of cramps, and their duration.

Results

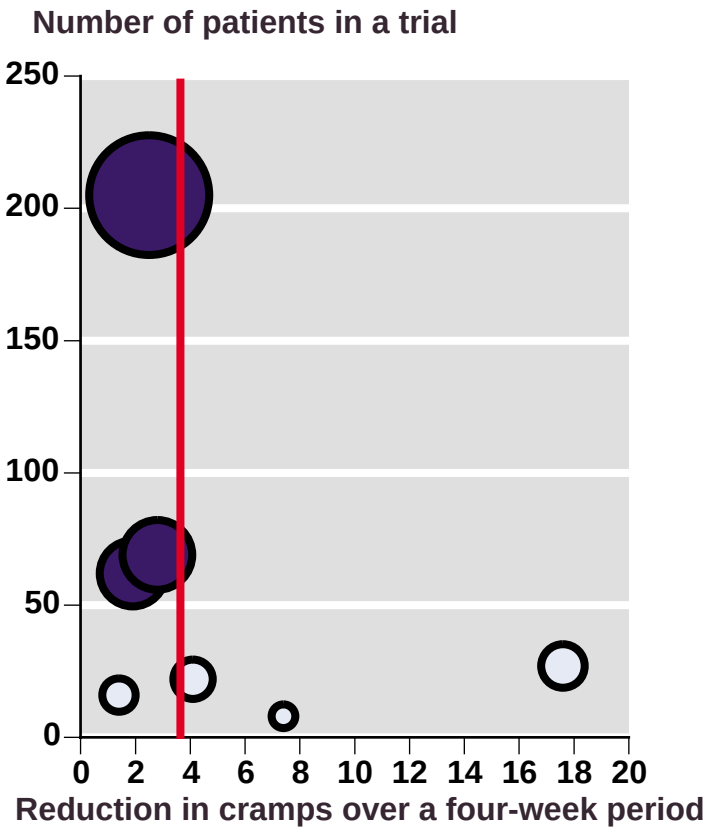
There were four published studies with 73 patients and three unpublished studies with 336 patients. The inclusion criteria meant that patients had to have more than two cramps a week. The dose of quinine was between 200 and 500 mg quinine, and the treatment period was one to four weeks (two weeks or more in six of the seven studies). All studies gave the number of cramps, six described their severity, and only one their duration.

With placebo the number of cramps in a four-week period (by extrapolation if studies were shorter) was 17 (about four a week) for all studies, 21 in the published studies and 16 in

Table 1: Results of published and unpublished randomised studies of quinine for nocturnal leg cramps

	Number of:		Over a four-week period (95% CI)	
	Trials	Patients	Cramps on placebo	Cramps avoided with quinine
Published	4	73	20.6 (14.9 to 26.6)	8.8 (4.2 to 13.5)
Unpublished	3	336	16.3 (14.7 to 17.9)	2.5 (0.2 to 5.6)
All	7	409	17.1 (15.4 to 18.8)	3.6 (2.2 to 5.1)

Figure 1: Individual trials of quinine (filled circles unpublished, open circles published)



the unpublished studies (Table 1). Quinine reduced the number of cramps in a four-week period by 4, 9 and 3 respectively (Table 1). There was also evidence that the severity of the cramps was reduced.

Published studies showed a greater effect than unpublished studies (Table 1). Larger studies showed lower and more consistent effects than small ones (Figure 1).

Tinnitus was the only adverse effect that occurred with significantly higher frequency when subjects took quinine rather than placebo (8 of 397 patients).

Comment

This is interesting stuff from a number of aspects. Firstly, it confirms that quinine is effective for nocturnal cramps. For someone who has about four cramps a week, quinine can be expected to reduce this to three a week.

There was clear publication bias. Unpublished trials had a smaller size of effect than published ones. But the published trials were small, and much of the extra effect came from two trials with 27 patients in one and eight in the other. The lesson may not be about publication bias, but the possibility of small trials, however well conducted, giving the wrong answer because of the random play of chance.

References:
1 M Man-Son-Hing & G Wells. Quinine for nocturnal leg cramps. A meta-analysis including unpublished data. Journal of General Internal Medicine 1998 13: 600-606.

How good is peer review?

Bandolier has been struck recently by an upsurge in questions about peer review and the importance of this process in "guaranteeing" quality. That will produce a wry smile in many who are reviewers, or have been the subject of review. Too often it seems to be a pretty haphazard process.

Reviewers are usually busy people, who try to help editors, their professional colleagues, and authors of papers by giving freely of their time to judge manuscripts, and to improve them. Many of us are grateful to reviewers who have helped improve our papers. But just as often unthinking, ignorant or insulting remarks by reviewers drive us to fury. What about the reviewer from a journal at the leading edge of evidence who dismissed a negative systematic review of a procedure because "*they tried it once and it seemed to work"!!* And the editor accepted it!!

All too often accepting or rejecting submitted papers seems to be little less than the random play of chance. A new study in neuroscience confirms just that [1].

Study

Two journals that routinely sent manuscripts to two reviewers allowed access to the assessments of these manuscripts. One journal provided information on all manuscripts over a six-month period (179), and the other provided information on 116 consecutive manuscripts. Both journals used a structured assessment, and assessors were asked to make the judgements:

- Should the manuscript be accepted, revised, or rejected?
- Was the priority for publication low, medium or high?

Agreement between reviewers was assessed using the kappa statistic. A value of 0 represents chance agreement, and a value of 1 perfect agreement. Scores of 0 to 0.2 are considered very poor, those between 0.2 and 0.4 poor, between 0.4 and 0.6 moderate, between 0.6 and 0.8 good and between 0.8 and 1 excellent.

Results

Agreement was not good (Table 1), and was not convincingly better than chance for either journal for acceptance, revision or rejection, or high, medium or low priority.

Table 1: Reviewers for two neuroscience journals failed to agree on quality and priority of manuscripts

	Interobserver agreement (kappa)	
Journal	Accept or reject	Priority
A	0.08 (-0.04 to 0.20)	-0.12 (-0.30 to 0.11)
B	0.28 (0.12 to 0.40)	0.27 (0.01 to 0.53)

Kappa values of 0 to 0.2 show very poor agreement, 0.2 to 0.4 poor, 0.4 to 0.6 moderate, 0.6 to 0.8 good and 0.8 to 1.0 excellent

Comment

Problems with peer review are not new. The paper has a lively discussion relating to other areas in science and medicine, and some of the attempts that have been made to improve matters. We can take some comfort from the fact that work is in progress to improve matters, but miracles are unlikely and peer review will remain a flawed process for some time to come. That means we have to accept that publication, and, often, grant applications, will remain something of a lottery.

It is a shame. It explains why complete rubbish appears in the best of journals, and why superb and important research can be hard to publish. The lesson is to keep submitting, because eventually by chance two reviewers will love it.

References:
1 PM Rothwell & CN Martyn. Reproducibility of peer review in clinical neuroscience. Is agreement between reviewers any greater than would be expected by chance alone? Brain 2000 123: 1964-1969.

MEASURING QUALITY OF PRESCRIBING FOR ASTHMA

What factors can be used as an indication of the overall quality of prescribing is one of those seemingly simple questions for which there are only complicated answers. For a start prescribed drugs are seldom just used for a single complaint. If they are used for many, that confuses things mightily. Then there's the population covered. GP practices in particular are subject to enormous differences in demography, wealth or deprivation, ethnicity, and the burden of disease. So when we see a paper that indicates that certain factors may relate to prescribing quality, even if they are preliminary [1], it deserves examination.

Study

The setting for the study was north Staffordshire. Two single-handed practices were chosen, one with a low ratio of corticosteroid to bronchodilator use (C:B ratio 0.24), and the other with a high ratio (C:B ratio 1.53). The practices were located within the same deprived area. These ratios had been calculated from an ***official*** database of all prescriptions issued by the practices between December 1993 and February 1994.

Patients from the practices who were prescribed drugs for asthma between March 1994 and August 1995 were found from a search of the ***practice*** databases. The patients were sent a validated questionnaire about the severity of their asthma symptoms during the previous month. They were also asked about smoking and occupation.

Patient notes were also examined to discover co-morbidity, and the strength of the diagnosis of asthma. Age and sex were also extracted, and a residential measure of deprivation calculated from the 1991 census for districts where patients lived.

Results

There were 366 patients prescribed asthma drugs in the two practices, about 7% of the list size in each practice. There was no difference between the age of patients, but there were differences in smoking, social class, deprivation score and diagnosis of comorbid conditions. About 80% of patients returned the questionnaire.

The symptom severity score was significantly higher in the low corticosteroid to bronchodilator practice (Figure 1). The difference remained after adjustments for age, sex, diagnosis, smoking and deprivation status.

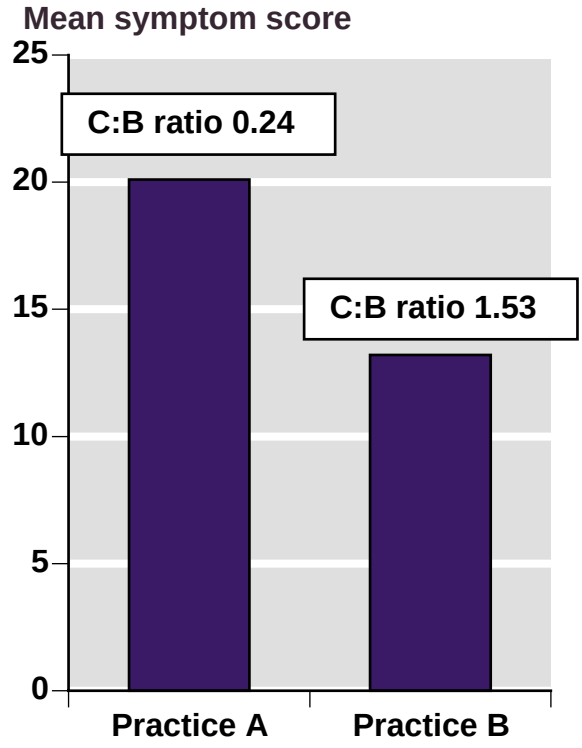
Comment

This paper is a really interesting read. It emphasises that these are preliminary results only, and from only two practices. But there are some interesting methods being used here, and the discussion puts them into context. Congratulations are in order for the sponsorship from the local hospital in Stoke on Trent.

Measuring the quality of prescribing has been a frequently-asked question of ***Bandolier***. So far there seems little good information, but perhaps we are not looking in the right place. We'd love to know if someone has some answers.

References:
1 M Shelley et al. Is the quality of asthma prescribing, as measured by the general practice ratio of corticosteroid to bronchodilator, associated with asthma morbidity? Journal of Clinical Epidemiology 2000 53: 1217-1221.

Figure 1: A higher ratio of corticosteroid to bronchodilator prescribing was associated with less severe asthma symptoms



Prevalence of AF

Bandolier is interested in common conditions, and in good evidence on prevalence and natural history of disease. Atrial fibrillation (AF) is just one of the common conditions that seems to creep up on us as we get older, and the number of people on warfarin is huge. So a report on the prevalence of the condition [1] is welcome, both because it gives us good information, but it also informs on how to get it.

Study

This was a cross-sectional study of adults older than 20 years enrolled in a large (1.9 million) health maintenance organisation in California. The enrolled population was examined to discover the number who had AF diagnosed in the 18 months between mid 1996 and end 1997.

Searching several automated clinical databases for a diagnosis of AF identified patients with atrial fibrillation. One database of electrocardiograms included all diagnoses for inpatient and outpatient electrocardiograms. Exclusion criteria were applied to identify only those with nontransient AF, and who were also health plan members in the source population. So transient AF after cardiac surgery was not included, nor AF relating to recent-onset hyperthyroidism.

The same databases were searched for five years beforehand for diagnoses of valvular heart disease, stroke, AF, coronary heart disease, hypertension and diabetes. Patient demographics were available, including ethnicity, for 89% of patients.

The denominator for the prevalence calculation was the adult population of plan members, and the results were presented both for the total population and by different age ranges.

Results

There were 17,974 adults with diagnosed, nontransient atrial fibrillation, and it was estimated by testing that 87% had AF confirmed by electrocardiogram. The overall prevalence in the 1.9 million members was 0.95% (95% confidence interval 0.94% to 0.96%). This increased with age from low levels in the under 55s to about 10% in the over-80s (Figure 1).

Prevalence was greater in men than in women (1.1% vs 0.8%), and among patients aged over 55 was more common in white (2.2%) than black (1.5%) patients.

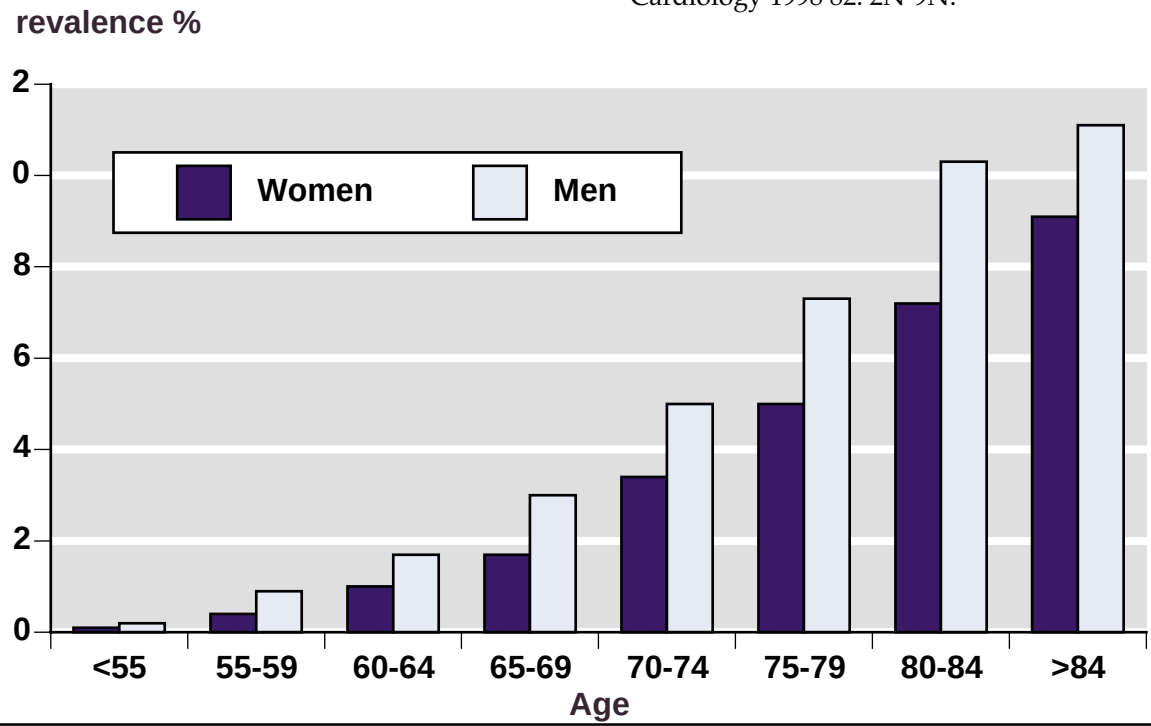
The paper also projected these figures to the whole population of the USA, both now and for the next 50 years. Based on the growth in older people expected over this period the number of people with AF in the USA was expected to grow from a current 2.3 million to 5.6 million by 2050.

Comment

One interesting feature of this paper is that it exemplified how the use of electronic databases, together with coding of disease, testing of data to ensure its quality, and a bit of thought can give interesting information on the ***amount*** of disease that we have to deal with. It is worth reading alongside two other recent reviews of AF [2,3] that give a wider perspective on the clinical implications of this disease burden.

References:
1 AS Go et al. Prevalence of diagnosed atrial fibrillation in adults. JAMA 2001 285:2370-2375.
2 SS Chugh et al. Epidemiology and natural history of atrial fibrillation: clinical implications. Journal of the American College of Cardiology 2001 37: 371-378.
3 WB Kannel et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. American Journal of Cardiology 1998 82: 2N-9N.

Figure 1: Prevalence of AF in California



Cholesterol fairy home to roost

In ***Bandolier*** 86 we asked why it was that we have to take our statins (usually) in the evening. We thought it might have been a simple pharmacokinetic explanation (short half-lives meaning that statins were more effective in the evening). Some of you wrote with the half-lives (many thanks), but pointed out that with time this should not matter much, even if cholesterol synthesis was higher at night.

Hard evidence was hard to find. What was required was a large study demonstrating that normal doses of evening statin produced convincingly lower cholesterol levels than normal doses of morning statin. A number of readers sent suggestions about papers we should read, and some of these we had read ourselves.

But even so, no convincing evidence. As best we can understand it, the evidence, such as it is, comes from a single study in Japan done 10 years ago [1]. It is a good study, but it doesn't answer the question.

Study

Patients with hyperlipidaemia (cholesterol at least 5.6 mmol/L) were allocated to one of five groups:

- Placebo
- 2.5 mg simvastatin in the morning
- 2.5 mg simvastatin in the evening
- 5 mg simvastatin in the morning
- 5 mg simvastatin in the evening

It was not stated whether allocation was randomised, but double-dummy methods maintained blinding. Fasting blood samples were taken at the end of a four-week placebo run in period (baseline) and then after 4, 8 and 12 weeks. A number of parameters were measured together at a single laboratory.

Results

The average total cholesterol was about 7 mmol/L in each of the five groups (29-31 patients per group), with standard deviations of about 1 mmol/L or so. Statins, but not placebo, caused falls in total and LDL-cholesterol (Figure 1) over the 12 weeks. Evening statin, and higher dose, were associated with lower total and LDL-cholesterol.

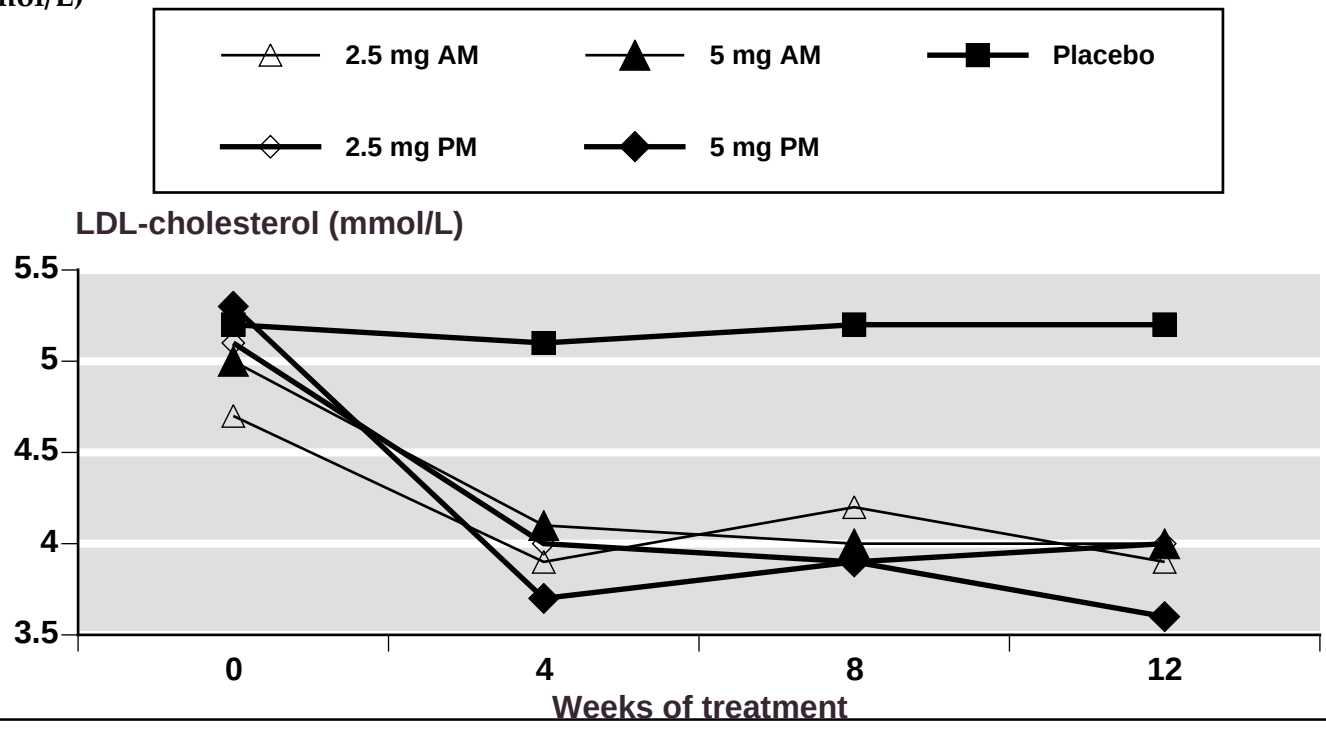
Comment

Are these differences credible, and is any credible difference worthwhile?

Credibility is stretched, somewhat. For instance, examine Figure 1, and remember that a standard deviation of over 1 mmol/L has to be superimposed on each of the numbers, meaning that plus and minus two standard deviations is 4 mmol/L when the mean is 4. Hmm! The statistics might tell us there are differences, but we have to strain to see them, so we are not greatly impressed.

Then there's the issue of dose. The 4S study (***Bandolier*** 15 [2]) had a target range for total cholesterol of 3.0 to 5.2 mmol/L for patients with similar starting cholesterol as here. That study used daily doses of 20 mg or 40 mg simvastatin (and 10 mg in two of 4000 patients). Prescribing Cost Analysis in primary care in England shows prescribed simvastatin as predominantly 10 mg and 20 mg tablets (with some 40 mg). So doses of 2.5 mg or 5.0 mg a day are unrepresentative of doses taken by our patients.

Figure 1: Changes in LDL-cholesterol over 12 weeks caused by different simvastatin regimens in groups of about 30 patients with initial total cholesterol above 5.6 mmol/L (average about 7.2 mmol/L)



So the evidence we have is this: in a relatively small number of patients, low doses of simvastatin taken in the evening produce slightly more reduction in cholesterol than when taken in the morning. What we do not have is a large study demonstrating that normal doses of evening statin produced convincingly lower cholesterol levels than normal doses of morning statin.

Given that most patients are likely to forget to take their statin in the evening some of the time, one wonders whether messing up dosing regimens for some theoretical benefit is worthwhile. Of course, there may be more convincing evidence, but we can't find it.

References:
1 Y Saito et al. Comparison between morning and evening doses of simvastatin in hyperlipidaemic subjects. A double-blind comparative study. Arteriosclerosis and Thrombosis 1991 11: 816-826.
2 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994 344: 1383-9.

INCREASING HANDWASHING IN HEALTHCARE WORKERS

Washing hands to reduce hospital acquired infection (***Bandolier*** 73) is an important topic examined before (***Bandolier*** 67, 82). Just to remind ourselves, in the UK hospital acquired infection costs about £1 billion a year, affects 1 patient in 10 in hospital, is responsible for the deaths of many more people than are road accidents, and use the resources of about 27 400-bed hospitals. And that's just the broad picture. At the margins, the effects on healthcare under pressure, as during Winter crises, the effects are much more than these stark assessments.

There's precious little around on handwashing that is easy to find, so when a systematic review about how to increase handwashing in healthcare workers [1] hoves into view it deserves some attention.

Review

The search was through, using four databases, searching the Internet, examining reference lists and attempting to identify unpublished work. Any study that aimed to promote handwashing in healthcare workers as a hospital infection control measure was included. Nearly 3000 citations were identified and examined.

Results

There were 21 studies fulfilling the inclusion criteria. Seventeen were uncontrolled studies and only two were randomised studies. Almost all (20/21) used observation to assess compliance with handwashing.

Handwashing – main themes

- Multifaceted approaches combining education, written material, reminders and continued feedback have the most marked and durable effect (see ***Bandolier*** 82).
- One-off educational approaches have a short term effect on handwashing behaviour, and the effect is not large.
- Strategically placed reminders have a modest but more sustained effect.
- Performance feedback can positively influence handwashing behaviour. Feedback must be repeated if the effect is to be maintained.
- Automated sinks can be beneficial, but the additional time involved may deter use.
- Moisturised soaps make little difference, but dry hand rubs near patients can give a small increased in frequency of decontamination.

The results of the studies are summarised in the box. Clearly it is the multifaceted approach that does best, as the recent example from Geneva (***Bandolier*** 82, not included in this review) showed.

Comment

It is remarkable, given the importance of hospital acquired infection, that more attention has not been given to studies of hand decontamination, so that we know what to do for the best to minimise this important problem. This review is an excellent start for those wanting to reduce our (and their) ignorance. None mentions water at over 60°C without mixer taps, or any other positive barriers to handwashing.

In decent studies (***Bandolier*** 67, 82) good handwashing initiatives can cut hospital acquired infections by about half. That is a big effect in a big problem. This review will benefit all those in secondary (and primary) care who want to deliver a safer and better service.

References:
1 S Naikoba, A Hayward. The effectiveness of interventions aimed at increasing handwashing in healthcare workers - a systematic review. Journal of Hospital Infection 2001 47: 173-180.

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